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This Month in *AJP*

Bone-Marrow-Derived Endothelial and Mesangial Cells Contribute to Glomerular Repair after Injury

Loss of glomerular cells and the defective repair of capillary damage in glomerular diseases are key factors in the progression to renal failure. During embryonic development the formation of new blood vessels, a process known as vasculogenesis, depends on endothelial precursor cells (EPCs) derived from the bone marrow. Recent data show that EPCs may be present in adult bone marrow and migrate to peripheral tissues to participapte in angiogenesis and injury repair. Rookmaaker et al (Am J Pathol 2003, 163:553–562) examined whether bone-marrow-derived EPCs would contribute to normal cell turnover in the glomerulus and participate in glomerular repair after injury. To conduct these studies they used a model of allogeneic bone marrow transplant to produce chimeric rats in which donor bone-marrow cells could be traced. In normal glomeruli of chimeric rats, a small number of endothelial and mesangial cells originated from donor bone-marrow cells. The proportion of bone-marrow-derived cells increased progressively during the 28 days after induction of glomerular injury. These cells were fully integrated in the glomerular structure, demonstrating that bone marrow EPCs can generate endothelial and mesangial cells necessary for glomerular repair in renal diseases.

Hepatitis C Virus Replication in Human Liver Studied by Digital Image Analysis

Infection with Hepatitis C Virus (HCV) is the most common cause of liver cirrhosis in the United States. Viral infection persists in about 80% of acutely infected individuals. Approximately 20% of chronically infected patients develop cirrhosis with increased risk to development of hepatocellular carcinoma. The progression of the infection is generally assessed by measurements of HCV serum titers. However, several studies have shown that there is no direct correlation between HCV serum titers and viral replication in the liver. Thus, measurement of HCV serum titers in chronically infected patients is probably an imprecise way to gauge the extent of liver disease and to evaluate disease progression or regression during treatment regimens. Chang et al (Am J Pathol 2003, 163:433–444) developed a digital analysis method to quantify HCV replication in the liver. The method is based on *in situ* hybrization with probes that are specific for the genomic and replicative forms of the virus. The authors calculated the maximal concentrations of genomic and replicative forms of the virus in single hepatocytes and observed dispersion of the virus in clusters of cells adjacent to virus-producing cells, suggesting that infection of neighboring hepatocytes may be a mechanism by which viral infection is maintained. The study also revealed that HCV replication occurred only in a small subset of cells, and that the level of replication was low. Nevertheless, the low replication level and restricted cell localization was sufficient to produce high serum titers of the virus.

Regulation of Collagen Transcription by Fli1, an Inhibitor Gene that Is Down-Regulated in Systemic Sclerosis

Collagen deposition is a complex process regulated by transcriptional and posttranscriptional mechanisms, and by the crosslinking of protein chains. Fibrosis depends on the balance between collagen deposition and degradation. Key to the pathogenesis of systemic sclerosis (scleroderma) is the increased production of collagen by dermal fibroblasts. Fli1 is a transcription factor that plays a role in hematopoiesis and vasculogenesis. It is a member of the Ets family and appears to be involved in extracellular matrix degradation. Kubo et al (Am J Pathol 2003, 163:571–581) hypothesized that Fli1 expression might be decreased in skin fibroblasts from patients with systemic sclerosis. They show that Fli1 is a physiological inhibitor of collagen gene expression in dermal fibroblasts. In contrast to normal human skin, Fli1 protein was not detectable in fibroblasts from systemic sclerosis patients. The study demonstrates that Fli1 is a suppressor of collagen transcription in human skin and that its down-regulation may be an important factor in the pathogenesis of systemic sclerosis.

Expression of PDGF-C in the Heart of Transgenic Mice Produces a Hypertrophic Phenotype and Dilated Cardiomyopathy

PDGF-C is a recently identified isoform in the PDGF family of growth factors. PDGFs are mitogenic agents for fibroblasts and may participate in angiogenesis. Ponten et al (Am J Pathol 2003, 163:673–682) developed transgenic mice that express PDGF-C under the control of the α-myosin heavy chain promoter. The mice developed cardiac fibrosis followed

by hypertrophy, whose progression was sex-dependent. In female but not in male mice the hypertrophic phenotype progressed to the development of dilated cardiomyopathy leading to heart failure and death. The heart of PDGF-C transgenic mice contained large vascular spaces and other vascular defects, suggesting the involvement of VEGF in the pathogenesis of the injury. These results offer new insights into the pathogenesis of cardiac hypertrophy and dilated cardiomyopathy, and establish a unique animal model for the study of these conditions.

Expression of the ATM Protein in B-Cell Malignancies

Progression through the cell cycle leading to cell replication is intimately related to mechanisms that regulate apoptosis and DNA repair. ATM (ataxia telangiectasia mutated) protein plays a major role in integrating DNA signals generated from DNA double-strand breaks with cell cycle progression. Patients with ATM inactivation have an increased risk of developing various types of malignancies, including B-cell derived neoplasias. Starczynski et al **(Am J Pathol 2003, 163:423–432)** analyzed the expression of ATM protein during lymphoid development and in B-cell malignancies. ATM has a complex pattern of expression during lymphoid development. During B-cell differentiation, it is highly expressed in pre- and postgerminal center B cells but is absent in germinal center B cells. Consistent with these observations, most tumors derived from germinal center cells did not express ATM. In contrast, tumors derived from pre- and postgerminal center cells showed either a high level of ATM expression or absence of expression, presumably caused by gene inactivation. The results indicate that immunostaining of ATM, as applied to the identification of lymphoid neoplasms, should be interpreted with caution because the patterns of staining may be related to the cell of origin rather than the malignancy itself.

Identification of Genes Expressed in Low-Grade Urothelial Carcinoma

A large number of studies have recently been published on the patterns of gene expression in urothelial carcinomas. However, most of the studies compare gene expression patterns at different stages of malignancy. Low-grade tumors rarely progress to malignancy but have a high frequency of recurrence. Thus, it is important to develop reliable diagnostic tools to identify these tumors. Diggle et al **(Am J Pathol 2003, 163:493–504)** used subtractive hybridization to compare gene expression between low-grade tumors and normal urothelium, in tissue samples obtained by laser-capture microdissection. The authors identified two genes that were overexpressed in low-grade tumors: 67LR (the 67-kd laminin receptor) and tumor-associated trypsin inhibitor (TATI). 67LR was expressed in the tumors but not in normal urothelium while TATI had a much more restricted expression in normal tissue than in tumors. TATI levels were elevated in the urine of patients with urothelial tumors. These studies demonstrate that laser-capture microdissection combined with methods of molecular analysis can be used to analyze the patterns of gene expression in small low-grade tumors and to develop markers for tumor diagnosis.